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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/732,919	12/10/2003	David J. Yang	UTSC:841US/10314647	7351

32425 7590 04/08/2009
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EXAMINER	
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ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
04/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/732,919	YANG ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5,14-17,23-28,31-51,60 and 61* is/are pending in the application.

4a) Of the above claim(s) *5,14-17,23-28 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,31-33,35-51,60 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/28/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 1/6/2009, in reply to the Office Action mailed 10/2/2008, is acknowledged and has been entered. Claims 1,3-4, 6-13,18-22,29-30 and 52-59 have been cancelled. Claim 61 is newly added. Claims 2, 31, 32, 35 and 42 have been amended. Claims 2, 5, 14-17, 23-28, 31-51, 60 and 61 are pending, of which claims 5, 14-17, 23-28 and 34 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 2, 31-33, 35-51, 60 and 61 are readable upon the elected invention and are examined herein on the merits for patentability.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 1/28/2009 was filed after the mailing date of the non-final rejection on 1/28/2009. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

Any rejection not reiterated herein has been withdrawn.

Applicant's arguments, with respect to the rejection of claims 1, 2, 31-33, 35-48, 51 and 60 under 35 USC 103(a) as being unpatentable over Iyer (*J. Nucl. Med.*, 2001, 42, p. 96-105) in view of Zareneyirzi (*Anti-Cancer Drugs*, 1999, 10, p. 685-692) have been fully considered but are moot in view of new grounds of rejection. Response to Applicant's arguments is incorporated into new grounds of rejection, set forth hereinbelow.

Applicant's arguments, with respect to the rejection of claims 1, 2, 31-33, 35-51 and 60 under 35 USC 103(a) as being unpatentable over Iyer (*J. Nucl. Med.*, 2001, 42, p. 96-105) in view of Zareneyirzi (*Anti-Cancer Drugs*, 1999, 10, p. 685-692), further in view of Belinka have been fully considered but are moot in view of new grounds of rejection. Response to Applicant's arguments is incorporated into new grounds of rejection, set forth hereinbelow.

Claim 38 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/672,763. Claims 42-51 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over the claims of copending Application No. 11/405,334 for reasons set forth in the previous Office Action.

New Grounds for Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 31-33, 35-38, 42-44 and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Taylor *et al.* (*J. Nucl. Med.*, 1997, 38, p. 821-826).

Taylor discloses that ^{99m}Tc-LL-EC is a new renal imaging agent with pharmacokinetic properties reported to be slightly superior to those with ^{99m}Tc-MAG3 (abstract). EC ligands were mixed with technetium-99m-sodium pertechnate in saline along with stannous chloride solution (page 821, right column). Imaging studies were performed in rats and humans (page 822). See also Figure 1. The compound ^{99m}Tc-ethylenedicysteine reads on the formula of the claims when R_{1-8} are H, R_9 is OH, R_{10} is OH, N is 0, m is 0, X is a bond, Y is a bond, and M is ^{99m}Tc. It is noted that the claims recite "a compound that comprises an N_2S_2 chelate conjugated to a targeting ligand of formula," as set forth in the claim. While Taylor does not specifically recite that his compound includes a "targeting agent," the compound ethylenedicysteine has all of the structural variables R_{1-10}, X,Y, n and m required by the instant claims, and is also known to concentrate in renal tissue, as such the compound ^{99m}Tc-ethylenedicysteine itself has at least some "targeting" properties to renal tissue.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 2, 31-33, 35-48, 51, 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer in view of Iyer (*J. Nucl. Med.*, 2001, 42, p. 96-105) in view of Zareneyirzi (*Anti-Cancer Drugs*, 1999, 10, p. 685-692), further in view of Yang *et al.* (*Ann. Nucl. Med. Sci.*, 2000, 13, p. 19-36).

Iyer discloses 8-[^{18}F]fluoropenciclovir (FPCV) for monitoring expression of herpes simplex virus 1 thymidine kinase (HSV1-kt) reporter gene in cell culture and in vivo (abstract). Penciclovir is used as a reporter probe for PET imaging (pages 95-96).

Iyer teaches ^{18}F labeling of penciclovir, rather than ^{99m}Tc labeling via an N_2S_2 chelator.

Zareneyirizi discloses synthesis of [^{99m}Tc]ethylenedicysteine-colchicine for evaluation of antinagiogenic effect. Colchicine, a potent antiangiogenic agent, is known to inhibit microtubule polymerization and cell arrest at metaphase. ^{99m}Tc labeled EC-COL was prepared to assess tumor microvascular density. Tissue distribution and planar imaging studies were evaluated in breast-tumor bearing rats (abstract). An amino analogue of cholchicine (COL-NH_2) was synthesized for conjugation to L,L-ethylenedicysteine (page 686, left column). See also Figure 1. Radiosynthesis of [^{99m}Tc]ethylenedicysteine-colchicine was achieved by addition of ^{99m}Tc into kit containing EC-COL, Na_2PO_4, ascorbic acid, and NaEDTA (page 686, right column). Zareneyirizi teaches that due to favorable physical characteristics as well as extremely low price, ^{99m}Tc has been preferred to label radiopharmaceuticals. Several compounds have been labeled with ^{99m}Tc using nitrogen and sulfur chelates. Bis-aminoethanethiol tetradentate ligands are known to form very stable Tc(V)O complexes on the basis of efficient binding fo the oxotechnetium group to two thiolsulfur and two amine nitrogen atoms. ^{99m}Tc-L,L-ethylenedicysteine ([^{99m}Tc]EC) is successful example of N_2S_2 chelates. EC can be labeled with ^{99m}Tc easily and efficiently with high radiochemical purity and stability, and is excreted through the kidney by active tubular transport (page 685, right column).

Yang discloses molecular targets for cancer imaging and therapy applications, including radionuclide imaging modalities (PET, SPECT) (page 19). Development of molecular nuclear medicine has been focused on the prediction of therapeutic response has focused on prediction of therapeutic response, differential diagnosis, and monitoring

tumor response to treatment. Because of favorable characteristics and low price (US $0.21/mCi vs. US$50/mCi of ^{18}F), ^{99m}Tc has been preferred to label radiopharmaceuticals. Bis-aminoethanethiol tetradentate ligands, also called diaminodithiol compounds are known to form very stable Tc(V)O complexes on the basis of efficient binding of the oxotechnetium group to two thiolsulfur and two amine nitrogen atoms. ^{99m}Tc-ethylenedicysteine (^{99m}Tc-EC) is a successful example of N_2S_2 chelates, and ^{99m}Tc-EC-drug conjugates were developed to characterize tumor tissues (page 20). Examples of 99mTc-EC-conjugates include those with folate, nitroimidazole, pentaglutamate, annexin, cholchine (see examples). Yang teaches that misonidazole is a hypoxic cell sensitizer, and labeling MISO with different radioisotopes (e.g. ^{18}F, ^{123}I, ^{99m}Tc) may be useful for differentiating a hypoxic but metabolically active tumor by PET or planar scintigraphy. 18F-fluoromisonidazole has been used with PET to evaluate hypoxia, however, the cost of using PET isotopes in a clinical setting is prohibitive. Although labeling MISO with iodine was the choice, high uptake in thyroid tissue was observed. Therefore, it is desirable to develop compounds for planar scintigraphy that the isotope is less expensive and easily available in most medical facilities (page 29-30). ^{99m}Tc-EC-NIM is disclosed, and scintigraphic imaging studies are performed (pages 21-22). It is further noted that Yang also discloses the following non-elected species as molecular markers for potential development in cancer detection: adenosine (page 19), quinazoline, thalidomide, VEGF, angiostatin (page 28-29).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute an alternative PET imaging radionuclide, e.g. ^{99m}Tc, for ^{18}F in the

methods of Iyer. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Zareneyirizi and Yang teach that ^{99m}Tc labeling of radiopharmaceuticals is preferred because of favorable physical characteristics as well as extremely low price compared to ^{18}F (page 685). One would have had a reasonable expectation of success in providing ^{99m}Tc in an ethylenedicysteine carrier, as Zareneyirizi and Yang teach that such complexes form stable chelates with oxotechnetium. Furthermore, one would have found it obvious to modify penciclovir via an amino group so as to conjugate to EC in a similar manner as colchicine was amino-modified for conjugation to EC, as in Zareneyirizi, Figure 1. Furthermore, it is well-known in the diagnostic arts to substitute one known reporter probe, or targeting moiety, for another. For example, Yang teaches substitution of ^{99m}Tc-EC for ^{18}F on nitroimidazole and benefits therefrom (page 21 and 29). For an example of substitution of various targeting moieties on a given radionuclide (^{99m}Tc-EC), Yang teaches conjugation of a variety of targeting moieties to EC, such as folate, nitroimidazole, pentaglutamate, annexin, colchine, etc. for imaging/therapy of various desired targets. As such, it would have been obvious to one of ordinary skill to substitute penciclovir-NH_2 for colchicine-NH_2 on the [^{99m}Tc]EC carrier disclosed by Zareneyrizi. Such a substitution would have yielded the expected result of PET imaging of in vivo HSVI-tk reporter gene expression via a targeted [^{99m}Tc]EC conjugate.

Applicant argues on pages 10-13 of the Response that the examiner has failed to establish a *prima facie* case of obviousness because the examiner has not set forth with

sufficient reason with rational underpinning as required by KSR to support a *prima facie* case of obviousness. Applicant asserts that Iyer teaches ^{18}F labeling of penciclovir, but that there is no rational basis as to one of ordinary skill would be motivated to replace the ^{18}F of Iyer with ^{99m}Tc-EC of Zareneyirzi. Applicant contends that nothing in Iyer teaches or suggests substituting ^{18}F with a chemical moiety such as a radiolabeled N_2S_2 chelate for imaging. Applicant further argues that the examiner argues that it is well-known in the diagnostic arts to substitute one reporter probe, or targeting moiety, for another but has no cited any evidence to support this assertion.

This is not found to be persuasive. The Yang reference is included in the rejection to demonstrate the well-known replacement of ^{99m}Tc-EC for ^{18}F on a given compound in the art.

Applicant further argues that Iyer focuses probes with single atom radiolabels, including ^{18}F, ^{124}I, ^{3}H labeled substrates, and that in fact Iyer suggests that substitution with a chemical moiety would not result in an effective reporter, which actually seems to teach away from the claimed invention. For example, on page 97, second full paragraph, Iyer teaches that slight structural variations have a significant effect on biological activity. In particular, Iyer teaches that "the lack of an ether oxygen in the side chain of PCV has a significant effect on its biological properties," even though PCV is "structurally similar to GCV." Page 97, second paragraph. Applicant asserts that thus, Iyer actually teaches away from substituting the single atom radiolabel (e.g., 18F) with a substantially larger moiety such as ^{99m}Tc-EC.

This is not found to be persuasive. Applicant's arguments regarding Iyer single atom radiolables have been fully considered. However, it is deemed that the Iyer reference does not reach the level of a teaching away from substitution of ^{99m}Tc-EC for ^{18}F, as suggested by Applicant. A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness; however, "the nature of the teaching is highly relevant and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) (Claims were directed to an epoxy resin based printed circuit material. A prior art reference disclosed a polyester-imide resin based printed circuit material, and taught that although epoxy resin based materials have acceptable stability and some degree of flexibility, they are inferior to polyester-imide resin based materials. The court held the claims would have been obvious over the prior art because the reference taught epoxy resin based material was useful for applicant's purpose, applicant did not distinguish the claimed epoxy from the prior art epoxy, and applicant asserted no discovery beyond what was known to the art.). Furthermore, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). See MPEP 2145. In the instant case, the Iyer reference merely teaches that slight structural modifications may affect biological activity, and thus it is considered that

Iyer does not specifically discredit or discourage some degree of structural modification, such as by conjugation of a chelating moiety.

Applicant further argues that one would not be motivated to substitute colchine of Zareneyrizi with penciclovir because Iyer does not teach that PCV is effective for imaging cells that do not express HSV-tk, and that there is nothing in Zarenyrizi to suggest that the mammalian cells/tumors that were evaluated therein were transfected with herpes virus. Applicant asserts that if anything Iyer teaches away from imaging cells of Zarenyrizi using ^{99m}Tc-EC-penciclovir.

This is not found to be persuasive. One of ordinary skill could readily substitute penciclovir as a targeting moiety for the purpose of imaging herpes transfected cells, as in Iyer, albeit with a different reporter (^{18}F).

Claims 2, 31-33, 35-51, 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer in view of Iyer (*J. Nucl. Med.*, 2001, 42, p. 96-105) in view of Zareneyirzi (*Anti-Cancer Drugs*, 1999, 10, p. 685-692) and Yang *et al.* (*Ann. Nucl. Med. Sci.*, 2000, 13, p. 19-36), further in view of further in view of Belinka (5,609,847).

The rejection over Iyer in view of Zareneyrizi and Yang is maintained as above.

Zareneyrizi teaches EDTA, rather than gluconate or glucarate, as a transchelator in the kit. However, gluconate and glucarate are well-known in the art to be functionally equivalent chelators to EDTA, as shown by Belinka.

Belinka discloses pharmaceutical kits can be prepared comprising a carrier, stabilizer, or preservative. A preferred kit would further comprise a predetermined amount of a reducing agent and a stabilizer that includes a transchelator. A transchelator as used herein denotes a chelating agent that is "weaker" than the constructs of the present invention. Thus, the transchelator stabilizes the reduced species of pertechnetate while allowing the construct to form a stable complex with the reduced metal. Suitable transchelators may be alkylenepolyaminocarboxylic acid compounds, such ethylenediaminetetraacetic acid (EDTA), hydroxyethylenediaminetriacetic acid (HEDTA), sodium glucoheptonate, sodium tartrate, sodium gluconate, etc. Depending on the nature of the metal eventually chosen, the kit can be used to prepare a radiodiagnostic agent or a radiotherapeutic agent (see column 19, lines 25-42).

It would have been obvious to one of ordinary skill in the art to substitute gluconate or glucarate for EDTA as functionally equivalent transchelators in the kit disclosed by Zareneyirizi. Such a substitution would have resulted in the predictable outcome of providing a metal transchelator in a kit for preparing a radionuclide.

The following references, drawn to non-elected species were found during the search for the elected species with regard to the targeting ligand. It should not be interpreted that a comprehensive search was performed for all non-elected species.

Claims 2, 31-33, 38 are rejected as being unpatentable over Sumita (*Radioisotopes*, 1988, 37(9), p. 502-8 (abstract), in view of Yang *et al.* (*Ann. Nucl. Med. Sci.*, 2000, 13, p. 19-36).

Sumita discloses evaluation of left ventricular function using ^{99m}-Tc diethylenetriamine-pentaacetic acid-human serum albumin (DTPA-HSA). ^{99m}Tc-DTPA-HAS was used for ECG gated blood pool scintigraphy (abstract).

Sumita teaches DTPA as a chelator to which HSA is conjugated and ^{99m}Tc is bound, rather than ethylenedicysteine.

Yang teaches that due to favorable physical characteristics and low price, ^{99m}Tc radionuclide has been the choice for labeling (page 19, left column). Although it has been reported that DTPA-drug conjugate could be labeled with ^{99m}Tc effectively, DTPA moiety does not chelate with ^{99m}Tc as stable as with ^{111}In. Bis-aminoethanethiol tetradentate ligands are known to form very stable Tc(V)O complexes on the basis of efficient binding of the oxotechnetium group to two thiolfulfur and two amine nitrogen atoms. ^{99m}Tc-ethylenedicysteine (^{99m}Tc-EC) is a successful example of an N_2S_2 chelate, and ^{99m}Tc-EC-drug conjugates have been developed to characterize tumor tissues, and may be useful in diagnostics and therapeutics (page 20, left column).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute ethylenedicysteine for DTPA in the ^{99m}Tc-DTPA-HSA conjugates of Sumita when the teaching of Sumita is taken in view of Yang. One would have been motivated to do so, and would have had a reasonable expectation of success in doing

so because Yang teaches that ethylenedicysteine is superior to DTPA in terms of ^{99m}Tc chelation stability.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS